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Abstract

Patients hospitalized for acute myocardial infarction (AMI) may have concomitant positive coronavirus disease 2019 (COVID-19). We aimed to compare the risk of in-hospital mortality in patients primarily hospitalized for AMI with or without concomitant COVID-19 positive status. Using the random-effects model, we conducted a systematic review and meta-analysis of published articles from December 1, 2019, to April 1, 2022. There were eight studies with 10,128 patients, including 612 patients with COVID and 9516 patients without COVID. A total of 261 patients (42.64%) with COVID-19 positive and 612 patients (6.43%) with negative COVID-19 status died in the hospital. Pooled data showed that patients with a primary diagnosis of AMI with COVID-19 infection had more than five times increased risk of in-hospital mortality compared to patients without COVID-19 (OR: 5.06, 95% CI: 3.61, 7.09; $I^2 = 35\%$, $P < 0.001$). However, pooled data from five studies with adjustment of baseline differences in patient demographics and characteristics, comorbidities, and in-hospital pharmacology revealed more than three times increased risk of in-hospital mortality compared to patients who had primary AMI without COVID-19 infection (aOR: 3.47, 95% CI: 2.21, 5.45; $I^2 = 0\%$, $P < 0.001$). In subgroup analysis, ST-elevation myocardial infarction (STEMI) had lower in-hospital mortality (OR 4.23, 95% CI: 3.31, 5.40; $I^2 = 0\%$, $P < 0.001$) compared to non-ST-segment elevation myocardial infarction (NSTEMI) (OR 9.97, 95% CI: 5.71, 17.41; $I^2 = 0\%$, $P < 0.001$) (p-value = 0.006). Our study shows that COVID-19 infection is associated with increased in-hospital mortality in patients with index hospitalization for AMI.

Keywords: COVID-19, Acute myocardial infarction, In-hospital mortality, Meta-analysis, Systematic review

1. Introduction

Coronavirus disease 2019 (COVID-19) is caused by Severe Acute Respiratory Syndrome. Coronavirus 2 (SARS-CoV-2), first reported in December of 2019, continues to mutate, causing the emergence of multiple new variants.[1,2] During this COVID-19 pandemic, patients primarily hospitalized for acute myocardial infarction (AMI) may have concomitant positive COVID-19 status. When patients are hospitalized with AMI, including ST-segment Elevation Myocardial Infarction (STEMI), the outcomes may differ based on the positive COVID-19 rate, regardless of acute respiratory failure, immediate coronary angiography, and pharmacotherapies.[3]

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Objective: To investigate whether COVID-19 positive status, regardless of symptoms, affects mortality outcomes in index hospitalizations for AMI by conducting a systematic review and meta-analysis comparing the cohort of patients with AMI without COVID-19. We conducted a systematic review and meta-analysis of published articles from December 1, 2019, to December 1, 2021. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for this review.[4]

2. Methods

We did not register the study protocol for this study.

Inclusion and Exclusion Criteria: We included all published English language studies on patients with index hospitalizations for AMI from December 1, 2019, to December 1, 2021. Among index hospitalization for AMI, patients with positive COVID-19 Polymerase Chain Reaction status were considered to have COVID-19 infection compared with AMI hospitalizations with a COVID-19 negative rate. We excluded studies conducted on non-hospitalized patients, case reports, case series, review articles, and meta-analyses. We also excluded non-comparison studies based on COVID-19 status. Since this is a non-interventional study, we didn't include randomized controlled trials.

Search Strategy and study selection: A comprehensive literature search was performed using PubMed, Embase, Google Scholar, and Web of Science for literature published within the defined period, including only human studies by PRISMA guidelines. We also reviewed the references of relevant articles for further studies. A staged literature search was performed, and all relevant articles were identified and included if appropriate after screening. The following pertinent keywords were used for search items; “COVID-19”, “coronavirus disease 2019”, “MI,” “Myocardial Infarction,” “ST-segment Elevation Myocardial Infarction,” “STEMI,” “Non-ST segment Elevation Myocardial Infarction,” “NSTEMI,” “Acute coronary syndrome,” A,” “Mortality,” and “Heart attack.” We have screened studies based on the above eligibility criteria using the PRISMA flow diagram.[4]

Data collection, process, items: Two reviewers (NB and SK) independently performed the literature sear, title, abstract, and a full-text text screening. Conflicts were resolved through consensus. We included both STEMI and NSTEMI as our variables of interest.

Quality assessment: We assessed the methodical rigor of the included studies using the modified Downs and Black checklist for cohort studies.[5] The checklist list has 27 items with a total possible score of 28. Studies were rated excellent if they scored above 25, promising if they scored between 20 and 25, fair if they scored between 15 and 19, and poor if they scored <15. Two independent investigators assessed each study, and discrepancies in scoring were resolved with consensus.

Outcomes and summary measure: The outcome work was in-hospital mortality in patients admitted with a primary diagnosis of AMI, with or without concomitant COVID-19. We used the odds ratio as the effect measure.

Analysis: Review Manager 5.4.0 software (the Cochrane Collaboration, Copenhagen, Denmark) was used for quantitative analysis. We used a random-effects model to calculate the odds ratio (OR and the corresponding 95% confidence interval (CI). We used the I^2 test to assess for heterogeneity.

3. Results

We identified 53 articles from MEDLINE/PUBMED and 43 from Embase and Web of Science. 57Farticlesen articles were screened, among which 23paperss were selected for complete text analysis. Finally, eight pieces were chosen for quantitative synthesis. Fig. 1 outlines the study selection process.

Baseline characteristics of Included Studies are shown in Table 2.

3.1. Assessment of methodological quality

The quality of each publication was evaluated using the Downs and Black questionnaire tool.[5] All of the studies were deemed fair due to the lack of blinding and confounder adjustment. None of the studies were excellent or good (Table 1).

3.2. Outcomes

Unadjusted -in-hospital mortality and subgroup analysis: There were 10,128 patients from eight studies, with 612 patients in the COVID-19 positive and 9516 patients in the COVID-19 negative group. A total of 261 patients (42.64%) with COVID-19 and 612 patients (6.43%) with negative COVID-19 status died in the hospital. Pooled data without adjustment for confounders showed that patients having AMI with COVID-19 infection had more than five times increased risk of in-hospital mortality compared to patients who had AMI without COVID-19 disorder (OR 5.06, 95% CI: 3.61, 7.09; $I^2 = 35\%$, $P < 0.001$).

Table 1. Downs and Black questionnaire tool for risk of bias assessment.

STUDY ID	Reporting										External Validity			Internal Validity						Confounding bias					P	Tot	Q.
Question No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27		
Case 2020	1	1	1	1	1	1	1	0	1	1	UTD	UTD	UTD	0	UTD	1	1	1	1	1	1	1	0	0	0	UTD	1	17	F*
Choudhry 2020	1	1	1	1	1	1	1	0	1	1	UTD	UTD	UTD	0	UTD	1	1	1	1	1	1	1	0	0	0	UTD	1	17	F
Popovic 2020	1	1	1	1	1	1	1	0	1	1	UTD	UTD	UTD	0	UTD	1	1	1	1	1	1	1	0	0	0	UTD	1	17	F
Solano-Lopez 2020	1	1	1	1	1	1	1	0	1	1	UTD	UTD	UTD	0	UTD	1	1	1	1	1	1	1	0	0	1	UTD	1	18	F
Little 2020	1	1	1	1		1	1	0	1	1	UTD	UTD	UTD	0	UTD	1	1	1	1	1	1	1	0	0	1	UTD	1	17	F
D'Ascenzo 2020	1	1	1	1		1	1	0	1	1	UTD	UTD	UTD	0	UTD	1	1	1	1	1	1	1	0	0	1	UTD	1	17	F
Rashid 2021	1	1	1	1	1	1	1	0	1	1	UTD	UTD	UTD	0	UTD	1	1	1	1	1	1	1	0	0	1	UTD	1	18	F
Saad 2021	1	1	1	1	1	1	1	0	1	1	UTD	UTD	UTD	0	UTD	1	1	1	1	1	1	1	0	0	1	UTD	1	18	F

F* = Fair, UTD: Unable to Determine.
P: Power. Q: Quality of studies. Tot: Total points of the study.

There were a total of 8529 patients in the STEMI subgroup, among which 524 patients were COVID-19 positive, and 8005 were COVID-19 negative. A total of 238 patients (45.42%) with COVID-19 and 557 patients (6.96%) with negative COVID-19 status died in the hospital in the STEMI subgroup. There were a total of1599 patients in the NSTEMI group, among which 88 patients were COVID-19 positive, and 1511 patients were COVID-19 negative. A total of 23 patients (26.14%) with COVID-19 and 55 patients (3.64%) with negative COVID-19 status died in the hospital in the NSTEMI subgroup. The subgroup of STEMI had lower in-hospital mortality (OR 4.23, 95% CI: 3.31, 5.40; $I^2 = 0\%$, $P < 0.001$) compared to NSTEMI (OR 9.97, 95% CI: 5.71, 17.41; $I^2 = 0\%$, $P < 0.001$). There was a statistically significant difference between the subgroups of STEMI and NSTEMI (P-value for subgroup difference = 0.006, $I^2 = 86.9\%$) (Fig. 2).

3.3. Adjusted in-hospital mortality

There were five studies in the adjusted group. The pooled data with adjustment of baseline differences in patient demographics and characteristics, comorbidities, and in-hospital pharmacology showed more than three times increased risk of in-hospital mortality in AMI with COVID-19 group compared with patients who had AMI without COVID-19 infection (aOR 3.47, 95% CI: 2.21, 5.45; $I^2 = 0\%$, $P < 0.001$) (Fig. 3).

Publication bias was assessed in the funnel plot, which showed the symmetrical scattering of studies suggesting no publication bias (Fig. 4).

3.4. Sensitivity analysis

We performed a sensitivity analysis to exclude individual studies; however, there was no significant change in the outcomes with the exclusion of individual studies.

4. Discussion

Our results show that COVID-19 positive status is associated with more than five times higher in-hospital mortality in patients admitted with AMI. Even after adjusting potential confounders (baseline differences in patient demographics and characteristics, comorbidities, and in-hospital pharmacology), pooling the adjusted odds ratio from the individual studies, the risk of in-hospital mortality was more than three times higher in the COVID-19 group compared to non-COVID-19. Moreover, our study shows that among COVID-19 subgroups, there are higher odds of mortality in the NSTEMI subgroup compared to STEMI.

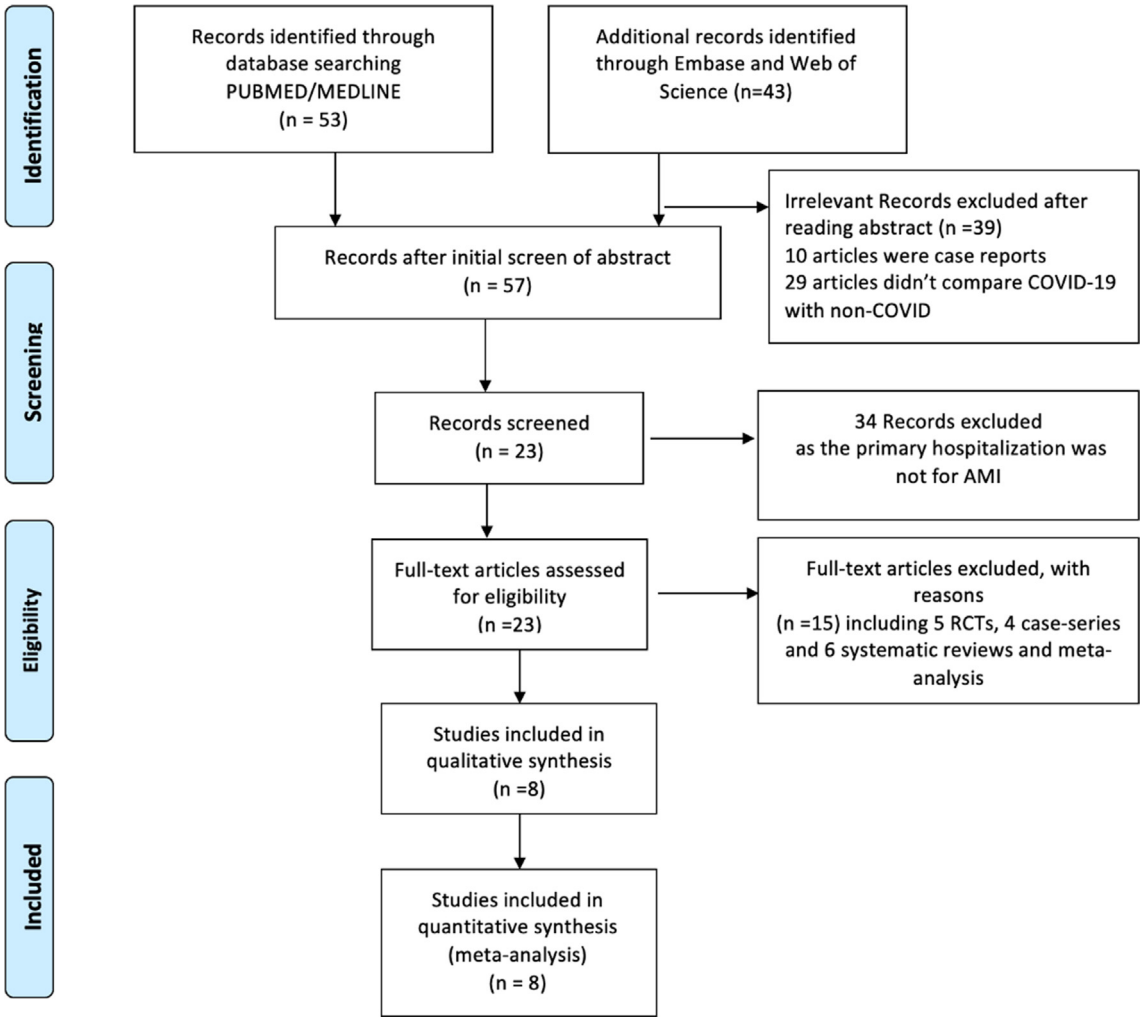

Fig. 1. PRISMA flow diagram of included studies. Abbreviations: PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Our findings contrast with a cohort study by Fardman et al., where STEMI patients admitted to ICU in the first wave of COVID-19-outbreak (March 9, 2020, through April 30, 2020) were compared with STEMI patients in ICU in the on-COVID-19 outbreak (March 9, 2018, through April 30, 2018), where there is no significant difference in in-hospital mortality. However, the patient population was not COVID-19 positive and only presented during the COVID-19 outbreak.[6] Another study by Gluckman et al., similar to our study, reported that in-hospital mortality increased in patients with AMI (STEMI) during the COVID-19 outbreak period after risk adjustment.[7] The increased mortality in the COVID-19 positive cohort may be due to higher comorbidities, older age, and racial disparity (more African Americans than Whites) compared to patients in the COVID-19 negative cohort.[7−10] COVID-19 induces multiple cytokines and chemokines, resulting in vascular inflammation, plaque instability, and myocardial inflammation.[11] Endothelial injury due to complement activation, hyper-viscosity, and increased procoagulants is associated with the hypercoagulable state in COVID-19 patients.[11−13] This increased inflammatory, prothrombotic, and procoagulant response in COVID-19, along with hypoxia and hemodynamic instability, may play an essential role in higher in-hospital mortality in the COVID-19 group when presented with AMI.[14] Although, acute hypoxic respiratory failure is the hallmark of severe COVID-19 disease, there have been diverse cardiovascular (CV) system manifestations including myocardial injury, heart failure, myocarditis, arrhythmia, and thromboembolism which further contribute to increased mortality in COVID-19 group.[1,3,6,8,10,15−22] An observational cohort study done in England demonstrated that the COVID-19 group was less likely to receive invasive angiography and percutaneous coronary intervention (PCI), which may be the reason for higher mortality, even after adjustment for

Table 2. Baseline Characteristics of studies included in meta-analysis.

Study Name and Year	Location and duration	Study design	Number of participants (N)	Mean age	PCI	Outcomes
Solano-Lopez 2020	Spain, March 15, 2020 to April 15, 2020	Prospective multicenter cohort study	N = 187 Male = 153	66.16	106 out of 111 patients with STEMI	In-hospital all-cause mortality, in-hospital Cardiovascular death with complication
Choudry 2020	Barts Hearts center London from March 1, 2020 to May 20, 2020.	Single centered observational study	N = 39 Male = 33	61.7	6	Length of stay, in-hospital mortality, ICU stay
Popovic 2020	France, February 26, 2020 to May 10, 2020	Prospective monocentric study	N = 83 Male:53	63.0.6	83	Length of stay, in-hospital mortality, procedural characteristics, inflammatory markers
Case 2020	MedStar health system, USA from March 1, 2020 to June 30, 2020	Prospective Cohort study	N = 1533 Male = 846	66.7	14	Length of stay, in-hospital mortality, procedural characteristics, inflammatory markers, use of mechanical ventilation
Little 2020	London, March 1 to April 30, 2020	Retrospective Observational	N = 348 Male: 278	63	All	Ambulance response times, time of PCI, Length of stay, In-hospital mortality
D'Ascenzo 2021	Northern-Italy, February 20, 2020 to May 3, 2020	Retrospective Observational multicenter	N = 779 Male = 576	68	More than 90% ACS patients	In-hospital all-cause mortality, in-hospital Cardiovascular death with complication
Rashid 2021	All Acute NHS hospitals in England from March 1, 2020 to May 31, 2020	Retrospective Observational Cohort Study	N = 12,958 Male = 8389	67.0	2077 in COVID ACS group and 71 in non-COVID ACS	In-hospital mortality and 30-day mortality
Saad (in-hospital) 2021	Vizient Clinical database from 757 US academic medical centers and affiliated hospitals	Retrospective Observational Cohort Study	N = 1008 (propensity matched) Male = 652	NA	3 primary PCI in covid-19 and 71 in non-covid = 19 group	Primary outcome is All-cause in-hospital mortality. Secondary outcomes were in-hospital composite death, recurrent MI or stroke, new acute decompensated heart failure, and cardiogenic shock

Abbreviations: PCI: Percutaneous Coronary Intervention ACS: Acute Coronary Syndrome STEMI: ST-segment Elevation Myocardial Infarction ICU: Intensive Care Unit USA: United States of America NHS: National Health System COVID: novel Corona Virus Disease NA: Not Applicable MI: Myocardial Infarction.

age, race, comorbidities and other confounders.[23] Popovic et al. reported that delayed hospital presentation leads to primary delayed PCI and a higher prevalence of myocardial infarction with the non-obstructive coronary artery (MINOCA) due to hypercoagulability in AMI patients with concomitant COVID-19 infection may have led to increasing in-hospital mortality.[16] Moreover, a recent meta-analysis by Rattka et al. reported a significant increase in door-to-balloon time in patients presenting with STEMI in the COVID-19 pandemic compared to STEMI in the pre-pandemic period. However, there were no differences in mortality. However, patients were not COVID-19 positive but presented in

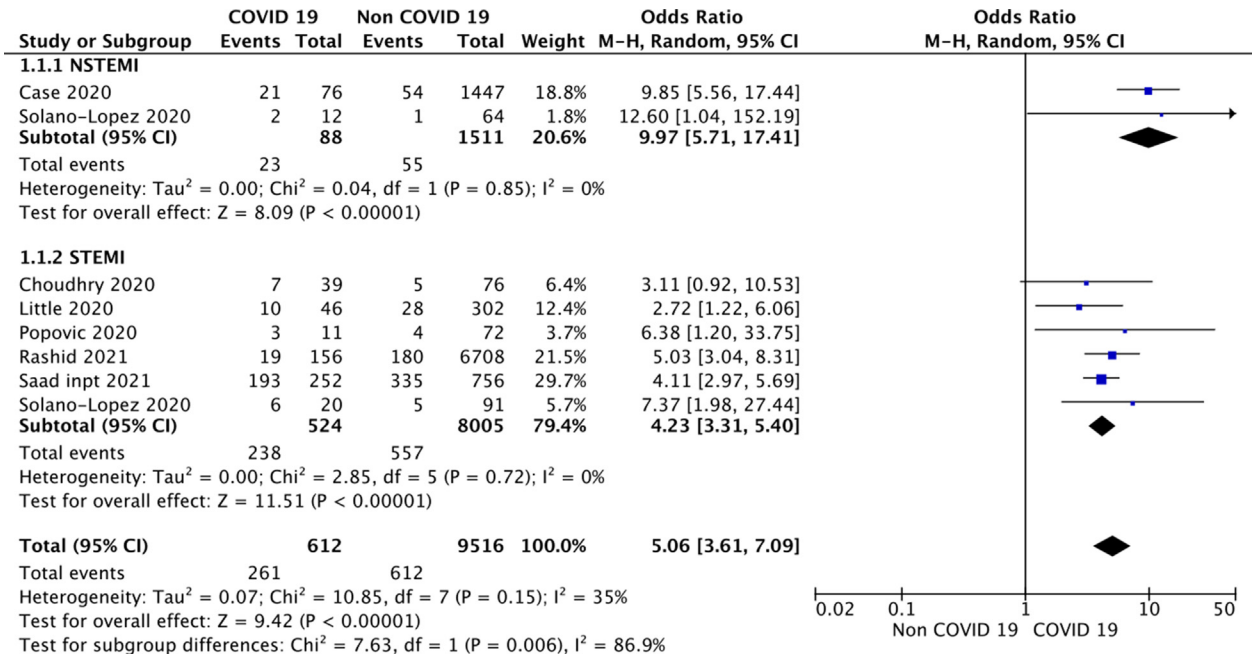

Fig. 2. Forest plot with subgroup analysis between NSTEMI and STEMI group showing odds ratios of in-hospital mortality in COVID-19 vs non-COVID-19 group. Abbreviations: NSTEMI: Non ST-segment Elevation Myocardial Infarction STEMI: ST-segment Elevation Myocardial Infarction.

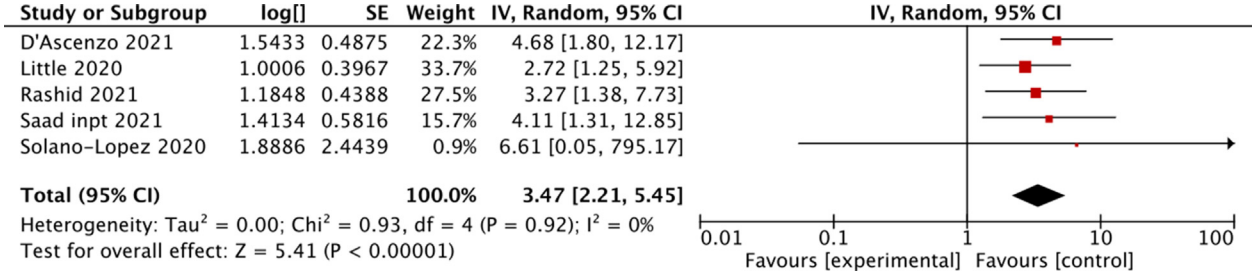

Fig. 3. Forest plot showing adjusted Odds ratio of in-hospital mortality between COVID-19 and non-COVID-19 group. Abbreviations: NSTEMI: Non ST-segment Elevation Myocardial Infarction STEMI: ST-segment Elevation Myocardial Infarction.

the pandemic period.[24] The cause of decreased mortality in the STEMI subgroup when compared to the NSTEMI subgroup may be due to prompt intervention with PCI.[8,23] NSTEMI subgroup included patients with severe conditions like sepsis, critical illness, and respiratory failure, which may be the cause of increased mortality in this subgroup and would not be differentiated from type I versus type II NSTEMI.[9,10,17] There was significant heterogeneity between the subgroups, which can be explained by the inclusion of type II NSTEMI in the NSTEMI group of this study.

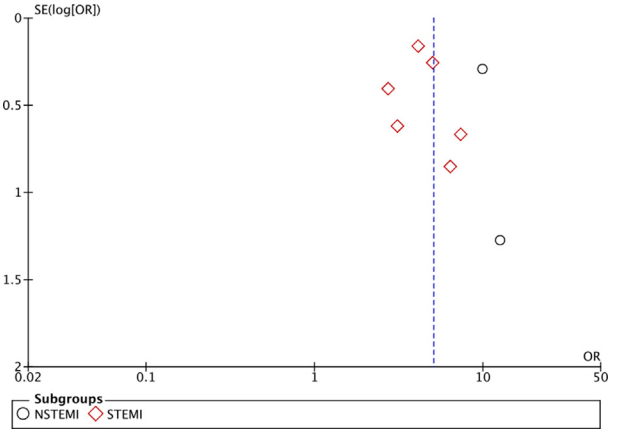

Fig. 4. Funnel plots to assess publication bias.

Our study is one of the few meta-analyses to answer the odds of in-hospital mortality in patients admitted with AMI with community-acquired COVID-19 compared to patients without COVID-19 infection. Since COVID-19 status was checked first on the initial presentation, we can say that the COVID-19 infections were mostly community-acquired rather than hospital-acquired. Previous meta-analyses mainly focused on the incidence of myocardial injury in patients primarily admitted with COVID-19. A

meta-analysis by Li et al. of 26 studies with 1,175,537 patients showed that myocardial infarction carries a higher risk of COVID-19 mortality.[19] However, our study is different from the study as we are looking into mortality from AMI rather than COVID-19 mortality. Our study is unique from other studies reporting the odds of in-hospital mortality in patients primarily admitted with AMI and having concomitant COVID-19 positive status.[25–27] Our study differs from a meta-analysis by Abate et al., which showed the odds of in-hospital mortality higher in COVID-19 patients with acute myocardial injury than in COVID-19 patients without acute myocardial injury. The comparison group is not COVID-19 but rather COVID-19 patients with or without myocardial injury.[28] With the high infection rate in hospitalized patients, our study highlights the importance of prompt recognition and treatment of COVID-19 in primary AMI hospitalization to improve in-hospital mortality.[1,8,21] Moreover, with the STEMI group having lower mortality, the role of primary PCI is further strengthened.[8,16,23] There are few studies directly comparing the in-hospital mortality in patients with a principal diagnosis of AMI with and without COVID-19 infection.

There are a few limitations to our study. Since the sample size is small, firm conclusions regarding the mortality risk in NSTEMI and STEMI subpopulations cannot be drawn. The meta-analysis included observational studies; there are unknown confounders that would not be adjusted. Only five of the eight studies adjusted for confounders. The quality of the included studies was only fair. We had eight studies that reported in-hospital mortality in patients primarily admitted with AMI, and only two studies reported data on NSTEMI. In addition, it is not only the low number of studies with NSTEMI patients but also the low number of NSTEMI patients with COVID-19 positivity (n = 88) that represents a limitation to our findings.

Moreover, due to the meta-analytic nature of the study, patient-level data could not be obtained. In the future, large-high-quality studies are needed to investigate the outcomes in these patient populations. Additionally, further studies are needed on the role of the COVID-19 vaccine and booster in this patient population. In hospitalized patients with a primary diagnosis of AMI, COVID-19 positive status is associated with higher in-hospital mortality in patients with NSTEMI and STEMI.

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Conflcits of interest

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